

We claim:

1. A targeting vector comprising:
  - a) a first sequence homologous to a portion or region of a target gene;
  - b) a second sequence homologous to a portion or region of a target gene;
  - c) a selectable marker cassette; and
  - d) a regulator, wherein the targeting vector is capable of modifying the target gene.
2. The targeting vector of claim 1, wherein the selectable marker cassette comprises a promoter region and a sequence encoding a selectable marker.
3. The targeting vector of claim 2, wherein the selectable marker is a marker conferring antibiotic resistance.
4. The targeting vector of claim 3, wherein the selectable marker conferring antibiotic resistance is a neomycin resistance gene.
5. The targeting vector of claim 2, wherein the promoter region comprises a promoter sequence.
6. The targeting vector of claim 5, wherein the promoter sequence is a PGK promoter sequence.
7. The targeting vector of claim 6, wherein the promoter region further comprises at least one operator sequence.
8. The targeting vector of claim 6, wherein the operator sequence is a lac operator sequence.
9. The targeting vector of claim 6, wherein the promoter region comprises the sequence set forth in SEQ ID NO:2.
10. The targeting vector of claim 1, wherein the regulator inhibits expression of the selectable marker.
11. The targeting vector of claim 1, wherein the regulator is positioned outside the first or second sequence substantially homologous to the target gene.
12. The targeting vector of claim 1, wherein the regulator comprises at least one repressor sequence.
13. The targeting vector of claim 12, wherein the repressor sequence is a lac repressor sequence.
14. The targeting vector of claim 13, wherein the regulator further comprises a nuclear localization signal.
15. The targeting vector of claim 14, wherein the regulator comprises the sequence set forth in SEQ ID NO:3.

16. The targeting vector of claim 1, wherein the regulator comprises a transcriptional silencer element.
17. The targeting vector of claim 14, wherein the nuclear localization sequence is positioned upstream of the repressor sequence.
18. A method of producing cells comprising a modification of a target gene, the method comprising:
- a) introducing into cells capable of homologous recombination a targeting vector, wherein the targeting vector comprises:
    - i) a first sequence homologous to a portion or region of the target gene;
    - ii) a second sequence homologous to a portion or region of the target gene;
    - iii) a selectable marker cassette; and
    - iv) a regulator;
  - b) selecting for cells expressing the selectable marker; and
  - c) identifying cells containing the modification of the target gene.
19. The method of claim 18, wherein the cells are embryonic stem cells.
20. A method of identifying cells comprising a disruption or modification of a target gene, the method comprising:
- a) introducing a targeting vector, wherein the targeting vector comprises:
    - i) a first sequence substantially homologous to a portion or region of the target gene;
    - ii) a second sequence substantially homologous to a portion or region of the target gene;
    - iii) a selectable marker cassette; and
    - iv) a regulator capable of controlling expression of a selectable marker, wherein the selectable marker is positioned within the selectable marker cassette; and wherein the targeting vector is capable of modifying the target gene;
  - b) selecting for cells expressing the selectable marker; and
  - c) identifying cells comprising the disruption or modification of the target gene.
21. The method of claim 22, wherein the cells are embryonic stem cells.
22. A method of enriching for cells comprising a disruption or modification of a target gene, the method comprising:
- a) inserting a targeting vector comprising:

- i) a first sequence substantially homologous to a portion or region of the target gene;
  - ii) a second sequence substantially homologous to a portion or region of the target gene;
  - iii) a selectable marker cassette; and
  - iv) a regulator capable of controlling expression of a selectable marker, wherein the selectable marker is positioned within the selectable marker cassette; and wherein the targeting vector is capable of modifying the target gene;
- b) selecting for cells in which the targeting vector has integrated into the genomes of the cells via homologous recombination, wherein the selected cells express the selectable marker; and
- c) identifying cells containing the disruption or modification of the target gene.
23. The method of claim ~~24~~, wherein the method enhances recovery of cells having the targeting vector integrated via homologous recombination into the genomes of the cells.
24. The method of claim 24, wherein the cells are embryonic stem cells.
25. The method of claim 24, wherein the targeting vector is introduced in the cells by electroporation.
26. An isolated host cell comprising a modification or disruption of a target gene, wherein the target gene is modified or disrupted by insertion of a targeting vector into the host cell.
27. A method of producing a transgenic animal having a genome comprising a modification or disruption of a target gene, the method comprising:
- a) introducing a targeting vector into a cell;
  - b) selecting cells expressing the selectable marker and identifying the cells containing the modification or disruption of the target gene;
  - c) inserting the cells identified in step (b) into an embryo; and
  - d) propagating the transgenic animal from the embryo.
28. A transgenic animal comprising a modification or disruption of a target gene within the genome of the transgenic animal, wherein the modification or disruption of the target gene is produced by:
- a) introducing a targeting vector into a cell;
  - b) selecting cells expressing the selectable marker and identifying the cells containing the modification or disruption of the target gene;

- c) inserting the cells identified in step (b) into an embryo ; and
- d) propagating the transgenic animal from the embryo.

29. A method of modifying or disrupting the function of a target DNA sequence, the method comprising introducing a targeting vector into a cell, thereby producing a homologous recombinant, wherein the function of the target gene is modified or disrupted, and wherein the targeting vector comprises:

- a) a first sequence homologous to a portion or region of the target DNA sequence;
  - b) a second sequence homologous to a portion or region the target DNA sequence;
  - c) a selectable marker cassette; and
  - d) a regulator capable of controlling expression of a selectable marker,
- wherein the selectable marker is positioned within the selectable marker cassette.

30. A method of producing an targeting vector, the method comprising:

- a) generating a first sequence homologous to a portion or region of a target DNA sequence;
- b) generating a second sequence homologous to a portion or region of a target DNA sequence;
- c) generating a selection marker cassette;
- d) generating a regulator;
- e) and cloning a, b, c, and d into a vector to produce a targeting vector.

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32, The method of claim 13, wherein the targeting vector comprises SEQ ID NO:13.